

ATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAG
TGCTGCCTGCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCG
CAGCGGCCTGGGGGGCGCCCCCTGGGGCTGCGGCTGCCCCGGGA
GACCGACGAAGAGCCCGAGGAGCCCGGCCGGAGGGGCGAGCTTTGT
GGAGATGGTGGACAACCTGAGGGGGCAAGTCGGGGGCAGGGGCTACTAC
GTGGAGATGACCGTGGGCAGCCCCCGCAGACGCTCAACATCCTGG
TGGATACAGGCAGCAGTAACTTTGCAGTGGGTGCTGCCCCCACCC
CTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGCACATACCGGG
ACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGA
AGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAAC
GTCAGTGTGCGTGCCAAACATTGCTGCCATCACTGAATCAGACAAGTT
CTTCATCAACGGCTCCAACCTGGGAAGGCATCCTGGGGCTGGCCTATG
CTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCT
CTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTG
TGGTGCTGGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTG
GAGGGAGCATGATCATTGGAGGTATCGACCACTCGCTGTACACAGGC
AGTCTCTGGTATACACCCATCCGGCGGGAGTGGTATTATGAGGTGAT
CATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGCA
AGGAGTACAACCTATGACAAGAGCATTGTGGACAGTGGCACCAACCAAC
CTTCGTTTGCCCAAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAG
GCAGCCTCCTCCACGGAGAAGTTCCCTGATGGTTTCTGGCTAGGAGA
GCAGCTGGTGTGCTGGCAAGCAGGCACCAACCCCTTGGAACATTTTCC
CAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCC
GCATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTG
GCCACGTCCCAAGACGACTGTTACAAGTTTGCCATCTCACAGTCATC
CACGGGCACTGTTATGGGAGCTGTTATCATGGAGGGCTTCTACGTTG
TCTTTGATCGGGCCCCGAAAACGAATTGGCTTTGCTGTCAGCGCTTGC
CATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTG
TCACCTTGGACATGGAAGACTGTGGCTACAACATTCCACAGACAGAT
GAGTCAACCCTCATGACCATAGCCTATGTCATGGCTGCCATCTGCGC
CCTCTTCATGCTGCCACTCTGCCTCATGGTGTGTGAGTGGCGCTGCC
TCCGCTGCCTGCGCCAGCAGCATGATGACTTTGCTGATGACATCTCC
CTGCTGAAG

FIG. 1A

CCATGCCGGCCCCCTCACAGCCCCGCCGGGAGCCCCGAGCCCCGCTGCCCAGG
CTGGCCGCCGCSGTGCCGATGTAGCGGGCTCCGGATCCCAGCCTCTCCCCT
GCTCCCGTGCTCTGCGGATCTCCCCTGACCGCTCTCCACAGCCCCGGACCCG
GGGGCTGGCCCAGGGCCCTGCAGGCCCTGGCGTCCTGATGCCCCCAAGCT
CCCTCTCCTGAGAAGCCACCAGCACCAACCAGACTTGGGGGCAGGCGCCA
GGGACGGACGTGGGCCAGTGCGAGCCCAGAGGGCCCCGAAGGCCGGGGCC
CACCATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAG
TGCTGCCTGCCACGGCACCCAGCACGGCATCCGGCTGCCCCCTGCGCAGC
GGCCTGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGAGACCGACG
AAGAGCCCCGAGGAGCCCCGGCCGGAGGGGCAGCTTTGTGGAGATGGTGGAC
AACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATGACCGTGGG
CAGCCCCCCCCGAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTT
TGCACTGGGTGCTGCCCCCACCCTTCTGCTGCTACTACCAGAGGCA
GCTGTCCAGCACATAACGGGACCTCCGGAAGGGTGTGTATGTGCCCTACAC
CCAGGGCAAGTGGGAAGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCC
ATGGCCCCAACGTCACTGTGCGTGCCAACATTGCTGCCATCACTGAATCAGA
CAAGTTCTTCATCAACGGCTCCAAGTGGGAAGGCATCCTGGGGCTGGCCTAT
GCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCTCTGG
TAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCTGG
CTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTGCGAGGGAGCATGAT
CATTGGAGGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCC
ATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCGGGTGGAGATCAAT
GGACAGGATCTGAAAATGGACTGCAAGGAGTACAACTATGACAAGAGCATTG
TGGACAGTGGCACCAACCAACCTTCGTTTGCCCAAGAAAGTGTGTTGAAGCTGC
AGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCTGATGGTTTC
TGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCAACCCTTGGAAC
ATTTTCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTT
CCGCATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGC
CACGTCCCAAGACGACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGC
ACTGTTATGGGAGCTGTTATCATGGAGGGCTTCTACGTTGTCTTTGATCGGG
CCCGAAAACGAATTGGCTTTGCTGTCAGCGCTTGCCATGTGCACGATGAGTT
CAGGACGGCAGCGGTGGAAGGCCCTTTGTACCTTGACATGGAAGACTG
TGGCTACAACATTCCACAGACAGATGAGTCAACCCTCATGACCATAGCCTAT
GTCATGGCTGCCATCTGCGCCCTCTTCATGCTGCCACTCTGCCTCATGGTGT
GTCAGTGGCGCTGCCTCCGCTGCCTGCGCCAGCAGCATGATGACTTTGCTG
ATGACATCTCCCTGCTGAAGTGAGGAGGCCCATGGGCAGAAGATAGAGATT
CCCCTGGACCACACCTCCGTGGTTCACCTTTGGTCACAAGTAGGAGACACAGA
TGGCACCTGTGGCCAGAGCACCTCAGGACCCTCCCCACCCACCAATGCCT
CTGCCTTGATGGAGAAGGAAAAGGCTGGCAAGGTGGGTTCCAGGGACTGTA
CCTGTAGGAAACAGAAAAGAGAAGAAAGAAGCACTCTGCTGGCGGGAATAC
TCTTGGTCACCTCAAATTTAAGTCGGGAAATTCTGCTGCTTGAACTTCAGCC
CTGAACCTTTGTCCACCATTCCTTTAAATTCTCCAACCCAAAGTATTCTTCTTT
TCTTAGTTTCAGAAGTACTGGCATCACACGCAGGTTACCTTGGCGTGTGTCC
CTGTGGTACCCTGGCAGAGAAGAGACCAAGCTTGTTTCCCTGCTGGCCAAA
GTCAGTAGGAGAGGATGCACAGTTTGCTATTTGCTTTAGAGACAGGGACTGT
ATAAACAAGCCTAACATTGGTGCAAAGATTGCCTCTTGAATT

FIG. 1B

MAQALPWLLLWMGAGVLP AHGTQH GIRLPLRSG LGGAPLGLRL
PRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPP
QTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVY
VPYTQGKWE GELGTDLVSIPHGPNTVRANIAAITESDKFFINGS
NWE GILGLAYAEIARPDDSLEPFFDSL VKQTHVPNLFSLQLCGAG
FPLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIV
RVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKS IK
AASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTN
QSFRITILPQQYL RPVEDVATSQDDCYKFAISQSSTGTVMGAVIM
EGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRLR
QQHDDFADDISLLK

FIG. 2A

ETDEEPEEPGRRGSFVEMVDNLRGKSGQGYVEMTVGSPPQT
LNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKG VYVP
YTQGWEGELGTDLV SIPHGPNVTVRANIAAITESDKFFINGSNW
EGILGLAYAEIARPDDSLEPFFDSL VKQTHVPNLFSLQLCGAGFP
LNQSEVLASVGGSMIIGGIDHS LYTGSLWYTPIRREWYYEVIIVRV
EINGQDLKMDCKEYNYDKSIVDSGTTNLR LPPKKVFEAAVKSIAA
SSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQ
SFRITILPQQYL RPVEDVATSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLR
QQHDDFADDISLLK

FIG. 2B

MAQALPWLLLWMGAGVLPAGHTQHGIRLPLRSGLGGAPLGLRL
PRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYVEMTVGSPP
QTLNILVDTGSSNFAVGAAPHPFLHRYRQRQLSSTYRDLRKGVY
VPYTQGKWEDELGTDLVSIHPGNVTVRANIAAITESDKFFINGS
NWEGLGLAYAEIARPDDSLEPFFDSL VKQTHVPNLFSLQLCGAG
FPLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIV
RVEINGQDLKMDCKEYNYDKSIVDSGTTNLR LPKKVFEAAVKSIIK
AASSTEKFPDGFVLGEQLVCWQAGTTPWNIFPVISLYLMGEVTN
QSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIM
EGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDEEDYKDDDDK

FIG. 3A

ETDEEPEEPGRRGSFVEMVDNLRGKSGQGYVEMTVGSPPQT
LNILVDTGSSNFAVGAAPHPFLHRYRQRQLSSTYRDLRKGVYVP
YTQGKWEDELGTDLVSIHPGNVTVRANIAAITESDKFFINGSNW
EGILGLAYAEIARPDDSLEPFFDSL VKQTHVPNLFSLQLCGAGFP
LNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRV
EINGQDLKMDCKEYNYDKSIVDSGTTNLR LPKKVFEAAVKSIIKAA
SSTEKFPDGFVLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQ
SFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDEEDYKDDDDK

FIG. 3B

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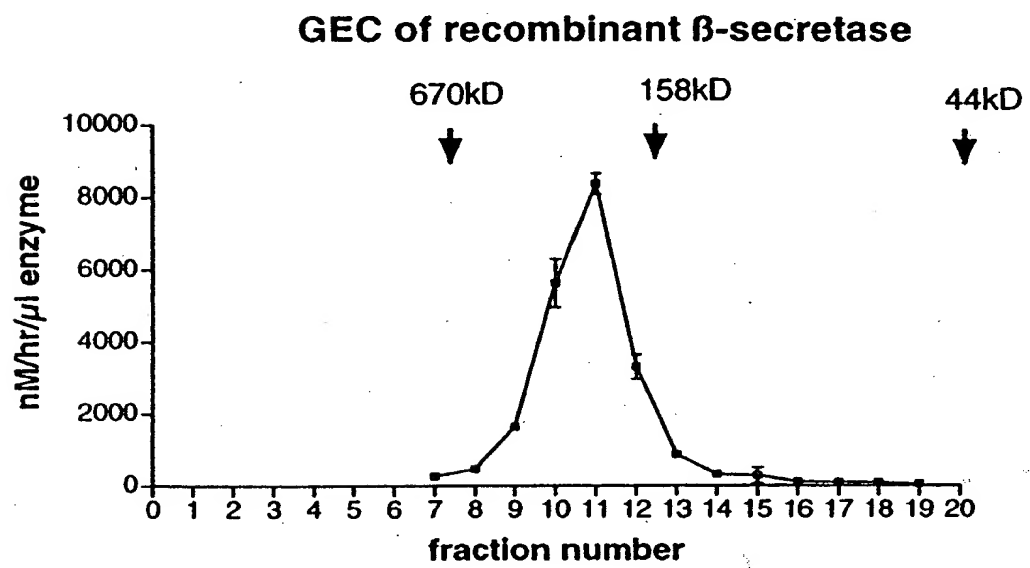


FIG. 4

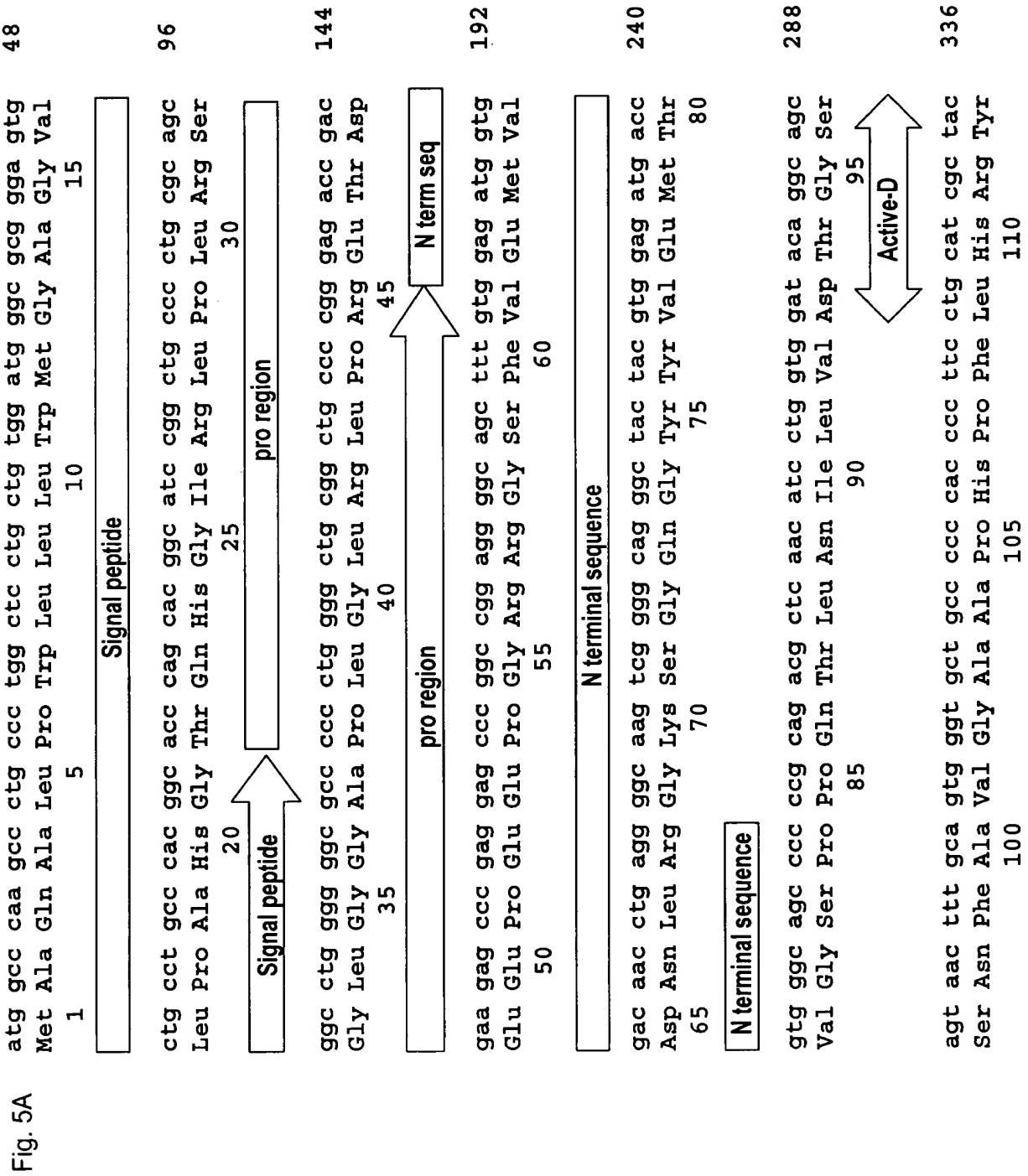


Fig. 5B

| | |
|---|-----|
| tac cag agg cag ctg tcc agc aca tac cgg gac ctc cgg aag ggt gtg Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val 115 120 125 | 384 |
| tat gtg ccc tac acc cag ggc aag tgg gaa ggg gag ctg ggc acc gac Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp 130 135 140 | 432 |
| ctg gta agc atc ccc cat ggc ccc aac gtc act gtg cgt gcc aac att Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile 145 150 155 160 | 480 |
| N-glycos | |
| gct gcc atc act gaa tca gac aag ttc ttc atc aac ggc tcc aac tgg Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp 165 170 175 | 528 |
| N-glycos | |
| gaa ggc atc ctg ggg ctg gcc tat gct gag att gcc agg cct gac gac Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp 180 185 190 | 576 |
| tcc ctg gag cct ttc ttt gac tct ctg gta aag cag acc cac gtt ccc Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro 195 200 205 | 624 |
| aac ctc ttc tcc ctg cag ctt tgt ggt gct ggc ttc ccc ctc aac cag Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln 210 215 220 | 672 |
| N-glycos | |

Fig. 5C

tct gaa gtg ctg gcc tct gtc gga ggg agc atg atc att gga ggt atc 720
 Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile
 225 230 235 240

N-gly

gac cac tcg ctg tac aca ggc agt ctc tgg tat aca ccc atc cgg cgg 768
 Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg
 245 250 255

gag tgg tat tat gag gtg atc att gtg cgg gtg gag atc aat gga cag 816
 Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln
 260 265 270

gat ctg aaa atg gac tgc aag gag tac aac tat gac aag agc att gtg 864
 Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val
 275 280 285

gac agt ggc acc acc aac ctt cgt ttg ccc aag aaa gtg ttt gaa gct 912
 Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala
 290 295 300

Active-D

gca gtc aaa tcc atc aag gca gcc tcc tcc acg gag aag ttc cct gat 960
 Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp
 305 310 315 320

ggt ttc tgg cta gga gag cag ctg gtg tgc tgg caa gca ggc acc acc 1008
 Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr
 325 330 335

Fig. 5D

| | |
|--|------|
| cct tgg aac att ttc cca gtc atc tca ctc tac cta atg ggt gag gtt Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val | 1056 |
| 340 | 345 |
| 350 | |
| acc aac cag tcc ttc cgc atc acc atc ctt ccg cag caa tac ctg cgg Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg | 1104 |
| 355 | 360 |
| 365 | |
| N-glycos | |
| cca gtg gaa gat gtg gcc acg tcc caa gac gac tgt tac aag ttt gcc Pro Val Glu Asp Val Ala Thr Ser Gln Asp Cys Tyr Lys Phe Ala | 1152 |
| 370 | 375 |
| 380 | |
| atc tca cag tca tcc acg gcc act gtt atg gga gct gtt atc atg gag Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu | 1200 |
| 385 | 390 |
| 395 | 400 |
| ggc ttc tac gtt gtc ttt gat cgg gcc cga aaa cga att ggc ttt gct Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala | 1248 |
| 405 | 410 |
| 415 | |
| gtc agc gct tgc cat gtg cac gat gag ttc agg acg gca gcg gtg gaa Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu | 1296 |
| 420 | 425 |
| 430 | |
| Internal peptide sequence | |

Fig. 5E

| | |
|---|------|
| ggc cct ttt gtc acc ttg gac atg gaa gac tgt ggc tac aac att cca | 1344 |
| Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn Ile Pro | |
| 435 440 445 | |
| cag aca gat gag tca acc ctc atg acc ata gcc tat gtc atg gct gcc | 1392 |
| Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met Ala Ala | |
| 450 455 460 | |
| Transmembrane | |
| atc tgc gcc ctc ttc atg ctg cca ctc tgc ctc atg gtg tgt cag tgg | 1440 |
| Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys Gln Trp | |
| 465 470 475 480 | |
| Transmembrane | |
| cgc tgc ctc cgc tgc ctg cgc cag cag cat gat gac ttt gct gat gac | 1488 |
| Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala Asp Asp | |
| 485 490 495 | |
| atc tcc ctg ctg aag tga | 1506 |
| Ile Ser Leu Leu Lys | |
| 500 | |

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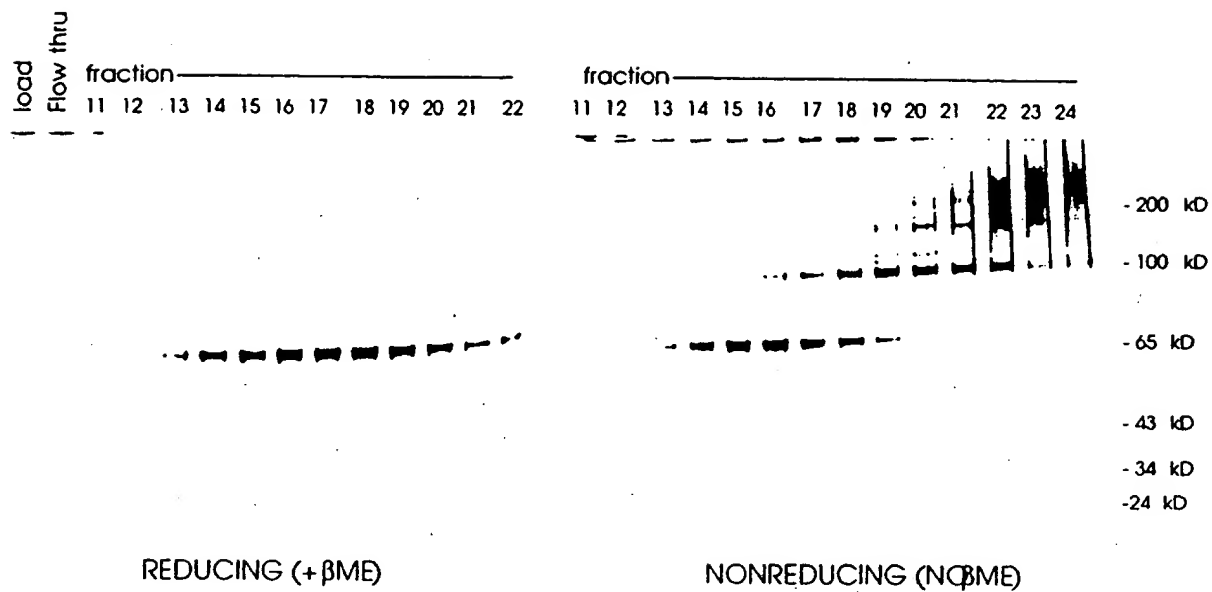


FIG. 6A

FIG. 6B

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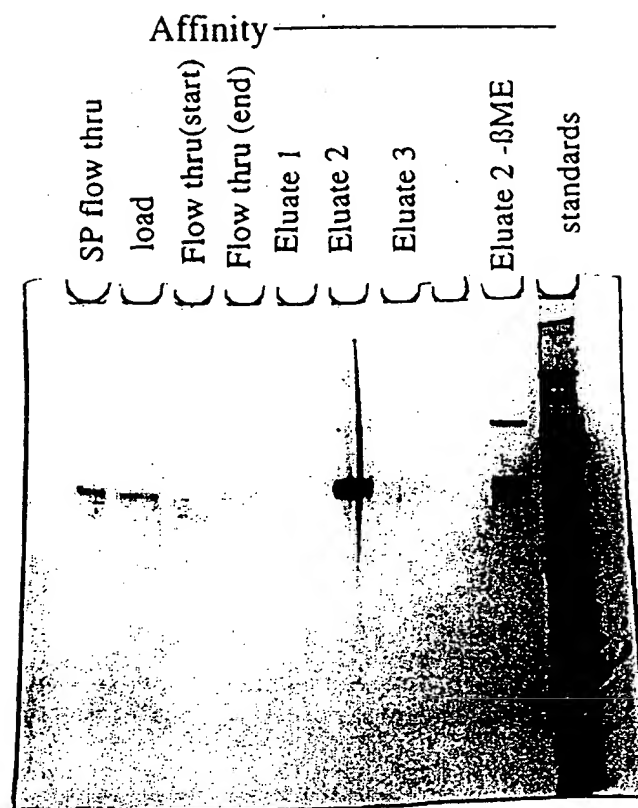


FIG. 7

SP flow thru
SP load
load
Flow thru
Eluate 1
Eluate 2
Eluate 3
293T standard

Affinity



FIG. 8

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E T D E E P E E P G R R G S F V E H V D N
 GARACNGAYGARGARCCNGARGARCCNGGNMGNMGNNGGNWSNTTYGTNGARATGGTNGAYAAY 63

3427-3430
 5' primer set 1

3431-3434
 3' primer set 1

3448-3451
 5' primer set 2

3452-3455
 3' primer set 2

1° HNC/primer set 1

(3428+3433)
 54 bp product

1° HNC & IMR32/ primer set 2

72 bp product
 sequence:

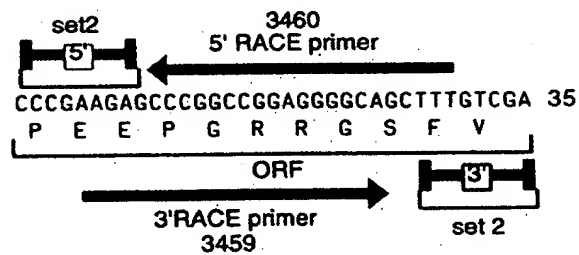


Fig. 9

| | | | | | |
|-------------|---|-----|-----|-----|-----|
| | 10 | 20 | 30 | 40 | |
| Hump501prot | M A Q A L P W L L L W M G A G V L P A H G T Q H G I R L P L R S G L G G A P L G | 40 | | | |
| Musp501prot | M A P A L H W L L L W V G S G M L P A Q G T H L G I R L P L R S G L A G P P L G | 40 | | | |
| | 50 | 60 | 70 | 80 | |
| Hump501prot | L R L P R E T D E E P E E P G R R G S F V E M V D N L R G K S G Q G Y Y V E M T | 80 | | | |
| Musp501prot | L R L P R E T D E E S E E P G R R G S F V E M V D N L R G K S G Q G Y Y V E M T | 80 | | | |
| | 90 | 100 | 110 | 120 | |
| Hump501prot | V G S P P Q T L N I L V D T G S S N F A V G A A P H P F L H R Y Y Q R Q L S S T | 120 | | | |
| Musp501prot | V G S P P Q T L N I L V D T G S S N F A V G A A P H P F L H R Y Y Q R Q L S S T | 120 | | | |
| | 130 | 140 | 150 | 160 | |
| Hump501prot | Y R D L R K G V Y V P Y T Q G K W E G E L G T D L V S I P H G P N V T V R A N I | 160 | | | |
| Musp501prot | Y R D L R K G V Y V P Y T Q G K W E G E L G T D L V S I P H G P N V T V R A N I | 160 | | | |
| | 170 | 180 | 190 | 200 | |
| Hump501prot | A A I T E S D K F F I N G S N W E G I L G L A Y A E I A R P D D S L E P F F D S | 200 | | | |
| Musp501prot | A A I T E S D K F F I N G S N W E G I L G L A Y A E I A R P D D S L E P F F D S | 200 | | | |
| | 210 | 220 | 230 | 240 | |
| Hump501prot | L V K Q T H V P N L F S L Q L C G A G F P L N Q S E V L A S V G G S M I I G G I | 240 | | | |
| Musp501prot | L V K Q T H I P N I F S L Q L C G A G F P L N Q T E A L A S V G G S M I I G G I | 240 | | | |
| | 250 | 260 | 270 | 280 | |
| Hump501prot | D H S L Y T G S L W Y T P I R R E W Y Y E V I I V R V E I N G Q D L K M D C K E | 280 | | | |
| Musp501prot | D H S L Y T G S L W Y T P I R R E W Y Y E V I I V R V E I N G Q D L K M D C K E | 280 | | | |
| | 290 | 300 | 310 | 320 | |
| Hump501prot | Y N Y D K S I V D S G T T N L R L P K K V F E A A V K S I K A A S S T E K F P D | 320 | | | |
| Musp501prot | Y N Y D K S I V D S G T T N L R L P K K V F E A A V K S I K A A S S T E K F P D | 320 | | | |
| | 330 | 340 | 350 | 360 | |
| Hump501prot | G F W L G E Q L V C W Q A G T T P W N I F P V I S L Y L M G E V T N Q S F R I T | 360 | | | |
| Musp501prot | G F W L G E Q L V C W Q A G T T P W N I F P V I S L Y L M G E V T N Q S F R I T | 360 | | | |
| | 370 | 380 | 390 | 400 | |
| Hump501prot | I L P Q Q Y L R P V E D V A T S Q D D C Y K F A I S Q S S T G T V M G A V I M E | 400 | | | |
| Musp501prot | I L P Q Q Y L R P V E D V A T S Q D D C Y K F A V S Q S S T G T V M G A V I M E | 400 | | | |
| | 410 | 420 | 430 | 440 | |
| Hump501prot | G F Y V V F D R A R K R I G F A V S A C H V H D E F R T A A V E G P F V T L D M | 440 | | | |
| Musp501prot | G F Y V V F D R A R K R I G F A V S A C H V H D E F R T A A V E G P F V T A D M | 440 | | | |
| | 450 | 460 | 470 | 480 | |
| Hump501prot | E D C G Y N I P Q T D E S T L M T I A Y V M A A I C A L F M L P L C L M V C Q W | 480 | | | |
| Musp501prot | E D C G Y N I P Q T D E S T L M T I A Y V M A A I C A L F M L P L C L M V C Q W | 480 | | | |
| | 490 | 500 | | | |
| Hump501prot | R C L R C L R Q Q H D D F A D D I S L L K | | | | 501 |
| Musp501prot | R C L R C L R H Q H D D F G D D I S L L K | | | | 501 |

FIG 10

FIG. 10

CTGTTGGGCTCGCGGTTGAGGACAAACTCTTCGCGGTCTTTCCAGTACTCT
 TGGATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCT
 GAGCGAGTCCGCATCGACCGGATCGGAAAACCTCTCGACTGTTGGGGTGAG
 TACTCCCTCTCAAAAGCGGGCATGACTTCTGCGCTAAGATTGTCAGTTTCC
 AAAAACGAGGAGGATTTGATATTCACCTGGCCCGCGGTGATGCCTTTGAGG
 GTGGCCGCGTCCATCTGGTCAGAAAAGACAATCTTTTTGTTGTCAAGCTTG
 AGGTGTGGCAGGCTTGAGATCTGGCCATACACTTGAGTGACAATGACATCC
 ACTTTGCCTTTCTCTCCACAGGTGTCCACTCCCAGGTCCAACCTGCAGGTCC
 ACTCTAGACCC

FIG. 11A

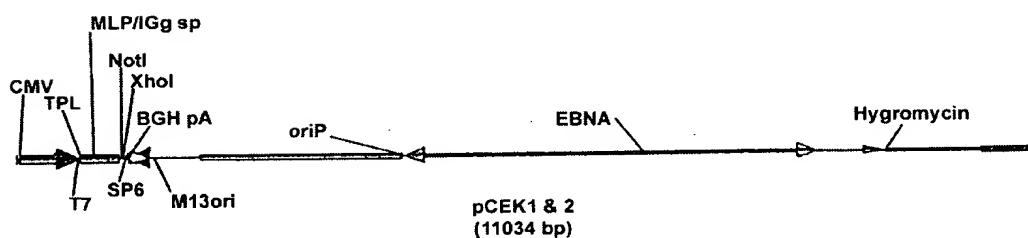


FIG. 11B

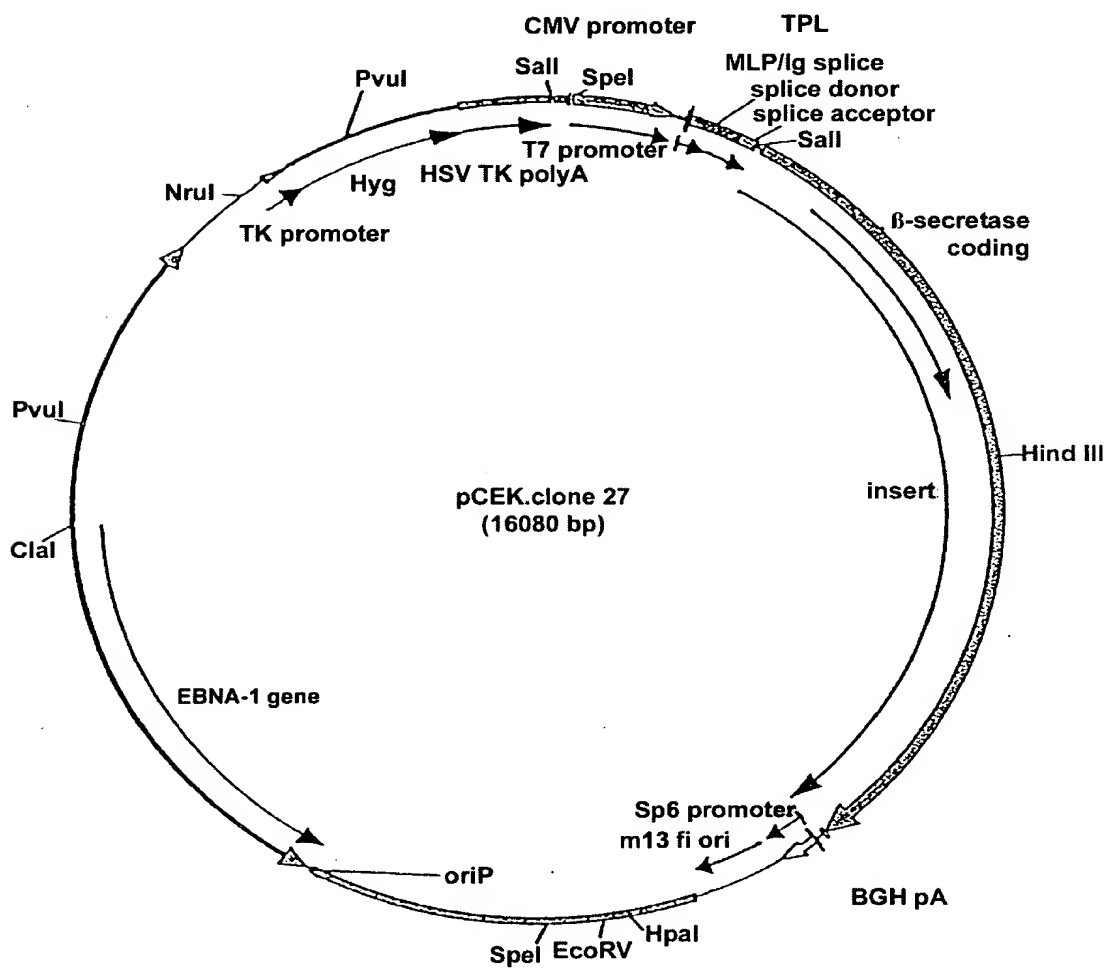


FIG. 12

Figure 13A

ttctcatggt tgacagctta tcatcgaga tccgggcaac gttgttgcat tgctgcaggc 60
 gcagaaactgg taggtatgga agatccgatg tacggggccag atatacgcgt tgacattgat 120
 SpeI
 tattgactag ttattaatag taatcaatta cgggggtcatt agttcatagc ccatatatgg 180
agttccgcgt tacataactt acggtaaatg gcccgccctgg ctgaccgccc aacgaccccc 240
gcccattgac gtcaataatg acgtatgttc ccatagtaac gccaataggg actttccatt 300
gacgtcaatg ggtggactat ttacgggtaaa ctgccactt ggcagtacat caagtgtatc 360
atatgccaaag tacgccccct attgacgtca atgacggtaa atggccccgc tggcattatg 420
cccagtacat gaccttatgg gactttccta cttggcagta catctacgta ttagtcatcg 480
ctattaccat ggtgatgcgg ttttggcagt acatcaatgg gcgtgggtag cggtttgact 540
cacggggatt tccaagtctc caccattg acgtcaatgg gagtttgttt tggcaccaaa 600
atcaacggga ctttccaaa tgctgtaaca actccgccc attgacgcaa atgggcggta 660
 ggcgtgtacg gtgggagggtc tataaagca gagctctctg gctaaactaga gaaccactg 720
 ctactggct tatcgaaatt aatacgactc actataggga gacccaagct ctgttgggct 780

Figure 13B

```

cgcggttgag gacaaactct tcgcggtctt tccagtactc ttggatcgga aaccgcgcgg 840
cctccgaacg gtactccgcc accgagggac ctgagcgagt ccgcatcgac cggatcggaa 900
                                     splice donor
aacctctga ctgttggggt gagtactccc tctcaaaagc gggcatgact tctgcgctaa 960
gattgtcagt ttccaaaaac gaggaggatt tgatatccac ctggccccgcg gtgatgcctt 1020
tgaggggtgc cgcgtccatc tggtcagaaa agacaatctt tttgttgtca agcttgaggt 1080
gtggcaggct tgagatctgg ccatacactt gagtgacaat gacatccact ttgcctttct 1140
                                     splice acceptor      Sall
ctccacaggt gtccactccc aggtccaact gcagggtcgac tctagaccgc gggaaattctg 1200
cagatatcca tcacactggc cgcactcgtc ccagccccgc ccgggagctg cgagccgcga 1260
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gctctccaca gccccgacc gggggctggc ccaggggccct gcaggccccct gcgtcctgat 1560
gcccccaagc tccctctcct gagaagccac cagcaccacc cagacttggg ggcaggcgcc 1620

```

Figure 13C

| | | |
|------|---|-------------|
| 1677 | aggacggac gtgggccagt gcgagcccag agggcccgaaggccggggcc cacc atg | Met |
| | | <u>1</u> |
| 1725 | gcc caa gcc ctg ccc tgg ctc ctg ctg tgg atg ggc ggc gga gtg ctg | |
| | Ala Gln Ala Leu Pro Trp Leu Leu Trp Met Gly Ala Gly Val Leu | 5 10 15 |
| 1773 | cct gcc cac gcc acc cag cac ggc atc cgg ctg ccc ctg cgc agc ggc | |
| | Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu Arg Ser Gly | 20 25 30 |
| 1821 | ctg ggg ggc gcc ccc ctg ggg ctg cgg ctg ccc cgg gag acc gac gaa | |
| | Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu Thr Asp Glu | 35 40 45 |
| 1869 | gag ccc gag gag ccc ggc cgg agg ggc agc ttt gtg gag atg gtg gac | |
| | Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu Met Val Asp | 50 55 60 65 |
| 1917 | aac ctg agg ggc aag tcg ggg cag ggc tac tac gtg gag atg acc gtg | |
| | Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu Met Thr Val | 70 75 80 |
| 1965 | ggc agc ccc ccg cag acg ctc aac atc ctg gtg gat aca ggc agc agt | |
| | Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr Gly Ser Ser | 85 90 95 |

Figure 13D

| | |
|---|------|
| aac ttt gca gtg ggt gct gcc ccc cac ccc ttc ctg cat cgc tac tac | 2013 |
| Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His Arg Tyr Tyr | |
| 100 105 110 | |
| cag agg cag ctg tcc agc aca tac cgg gac ctc cgg aag ggt gtg tat | 2061 |
| Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr | |
| 115 120 125 | |
| gtg ccc tac acc cag gcc aag tgg gaa ggg gag ctg ggc acc gac ctg | 2109 |
| Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu | |
| 130 135 140 145 | |
| gta agc atc ccc cat gcc ccc aac gtc act gtg cgt gcc aac att gct | 2157 |
| Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala | |
| 150 155 160 | |
| gcc atc act gaa tca gac aag ttc ttc atc aac ggc tcc aac tgg gaa | 2205 |
| Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu | |
| 165 170 175 | |
| ggc atc ctg ggg ctg gcc tat gct gag att gcc agg cct gac gac tcc | 2253 |
| Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser | |
| 180 185 190 | |
| ctg gag cct ttc ttt gac tct ctg gta aag cag acc cac gtt ccc aac | 2301 |
| Leu Glu Pro Phe Phe Asp Ser Ser Leu Val Lys Gln Thr His Val Pro Asn | |
| 195 200 205 | |

Figure 13E

| | |
|---|------|
| ctc ttc tcc ctg cag ctt tgt ggt gct ggc ttc ccc ctc aac cag tct Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser 210 215 220 225 | 2349 |
| gaa gtg ctg gcc tct gtc gga ggg agc atg atc att gga ggt atc gac Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp 230 235 240 | 2397 |
| cac tcg ctg tac aca ggc agt ctc tgg tat aca ccc atc cgg cgg gag His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu 245 250 255 | 2445 |
| tgg tat tat gag gtc atc att gtg cgg gtg gag atc aat gga cag gat Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp 260 265 270 | 2493 |
| ctg aaa atg gac tgc aag gag tac aac tat gac aag agc att gtg gac Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp 275 280 285 | 2541 |
| agt ggc acc acc aac ctt cgt ttg ccc aag aaa gtg ttt gaa gct gca Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala 290 295 300 305 | 2589 |
| gtc aaa tcc atc aag gca gcc tcc tcc acg gag aag ttc cct gat ggt Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly 310 315 320 | 2637 |

Figure 13F

| | | | | |
|------|---|-----|-----|-----|
| 2685 | ttc tgg cta gga gag cag ctg gtg tgc tgg caa gca ggc acc acc cct | 325 | 330 | 335 |
| | phe trp leu gly glu gln leu val cys trp gln ala gly thr thr pro | | | |
| 2733 | tgg aac att ttc cca gtc atc tca ctc tac atg ggt gag gtt acc | 340 | 345 | 350 |
| | trp asn ile phe pro val ile ser leu tyr leu met gly glu val thr | | | |
| 2781 | aac cag tcc ttc cgc atc acc atc ctt ccg cag caa tac ctg cgg cca | 355 | 360 | 365 |
| | asn gln ser phe arg ile thr ile leu pro gln gln tyr leu arg pro | | | |
| 2829 | gtg gaa gat gtg gcc acg tcc caa gac gac tgt tac aag ttt gcc atc | 370 | 375 | 380 |
| | val glu asp val ala thr ser gln asp cys tyr lys phe ala ile | | | 385 |
| 2877 | tca cag tca tcc acg ggc act gtt atg gga gct gtt atc atg gag ggc | 390 | 395 | 400 |
| | ser gln ser ser thr gly thr val met gly ala val ile met glu gly | | | |
| 2925 | ttc tac gtt gtc ttt gat cgg gcc cga aaa cga att ggc ttt gct gtc | 405 | 410 | 415 |
| | phe tyr val val phe asp arg ala arg lys arg ile gly phe ala val | | | |
| 2973 | agc gct tgc cat gtg cac gat gag ttc agg acg gca gcg gtg gaa ggc | 420 | 425 | 430 |
| | ser ala cys his val his asp glu phe arg thr ala ala val glu gly | | | |

Figure 13G

| | |
|---|------|
| cct ttt gtc acc ttg gac atg gaa gac tgt ggc tac aac att cca cag | 3021 |
| Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn Ile Pro Gln | |
| 435 440 445 | |
| <hr/> | |
| aca gat gag tca acc ctc atg acc ata gcc tat gtc atg gct gcc atc | 3069 |
| Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met Ala Ala Ile | |
| 450 455 460 465 | |
| <hr/> | |
| tgc gcc ctc ttc atg ctg cca ctc tgc ctc atg gtg tgt cag tgg cgc | 3117 |
| Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys Gln Trp Arg | |
| 470 475 480 | |
| <hr/> | |
| tgc ctc cgc tgc ctg cgc cag cag cat gat gac ttt gct gat gac atc | 3165 |
| Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala Asp Asp Ile | |
| 485 490 495 | |
| <hr/> | |
| tcc ctg ctg aag tga ggaggcccat gggcagaaga tagagattcc cctggaccac | 3220 |
| Ser Leu Leu Lys | |
| 500 | |
| <hr/> | |
| acctccgtgg ttcactttgg tcacaagtag gagacacaga tggcacctgt ggccagagca | 3280 |
| <hr/> | |
| cctcaggacc ctcccacc accaaatgcc tctgccttga tggagaagga aaaggctggc | 3340 |
| <hr/> | |
| aaggtaggtt ccagggactg tacctgtagg aaacagaaaa gagaagaaag aagcactctg | 3400 |
| <hr/> | |
| ctggcgggaa tactcttggg cacctcaaat ttaagtcggg aaattctgct gcttgaaact | 3460 |
| <hr/> | |

Figure 13H

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catctcagaa gatgggtgtt gttttcaatg ttttctttc tgtggttgca gcctgaccaa 3940
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aggaataggt aggagacctc ttctatctaa tccttaaaag cataatgttg aacattcatt 4300

HindIII

Figure 13I

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Figure 13J

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Figure 13K

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Figure 13L

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 HpaI
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Figure 13M

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Figure 13N

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Figure 130

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Figure 13P

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Figure 13Q

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Figure 13R

ClalI

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ctcaacacgc gtaagatcct tgagagtttt cgccccgaag aacgttttcc aatgatgagc 12340
actttttaaag ttctgctatg tggcgcggta ttatcccgtg ttgacgccgg gcaagagcaa 12400
ctcggtcgcc gcatacacta ttctcagaat gacttgggtg agtactcacc agtcacagaa 12460
aagcatctta cggatggcat gacagtaaga gaattatgca gtgctgccat aaccatgagt 12520
gataacactg cggccaactt acttctgaca acgatcggag gaccgaagga gctaaaccgt 12580
tttttgcaca acatggggga tcatgtaact cgccttgatc gttgggaacc ggagctgaat 12640
gaagccatac caaacgacga gcgtgacacc acgatgcctg cagcaatggc aacaacgttg 12700

Figure 13S

cgcaaatat taactggcga actactact ctagtctccc ggcaacaatt aatagactgg 12760
atggaggcgg ataaagtgc aggaccactt ctgcgctcgg cccttccggc tggctggttt 12820
attgctgata aatctggagc cggtgagcgt gggctctcgg gtatcattgc agcactgggg 12880
ccagatggta agccctcccg tatcgtagtt atctacacga cggggagtca ggcaactatg 12940
gatgaacgaa atagacagat cgctgagata ggtgcctcac tgattaagca ttggtaactg 13000
tcagaccaag ttactcata tatactttag attgattaa aacttcattt ttaatttaa 13060
aggatctagg tgaagatcct ttttgataat ctcatgacca aaatccctta acgtgagttt 13120
tcgttccact gagcgtcaga cccgtagaa aagatcaaag gatcttcttg agatcccttt 13180
tttctgcgcg taatctgctg cttgcaaca aaaaaaccac cgctaccagc ggtggtttgt 13240
ttgccggatc aagagctacc aactctttt ccgaaggtaa ctggcttcag cagagcgag 13300
ataccaata ctgtccttct agtgtagccg tagttaggcc accacttcaa gaactctgta 13360
gcaccgccta catacctgc tctgctaata ctgttaccag tggctgctgc cagtggcgat 13420
aagtcgtgtc ttaccgggtt ggactcaaga cgatagttac cggataaggc gcagcggtcg 13480
ggctgaacgg ggggttcgtg cacacagccc agcttggagc gaacgacctt caccgaactg 13540

Figure 13T

agatacctac agcgtgagct atgagaaagc gccacgcttc ccgaaggagg aaagcgggac 13600
 aggtatccgg taagcggcag ggtcggaaaca ggagagcgca cgagggagct tccaggggga 13660
 aacgcctggt atctttatag tcctgtcggg ttctgccacc tctgacttga gcgtcgattt 13720
 ttgtgatgct cgtcaggggg gcggagcccta tggaaaaacg ccagcaacgc ggccttttta 13780
 cggttccctgg ccttttgctg cgccgcgtgc ggctgctgga gatggcggac gcgatggata 13840
 tgttctgcca agggttggtt tgcgcattca cagttctccg caagaattga ttggctccaa 13900
 ttcttggagt ggtgaatccg ttagcgaggt gccgccggct tccattcagg tcgagggtggc 13960
 ccggctccat gcaccgcgac gcaacgcggg gaggcagaca aggtataggg cggcgccctac 14020
 aatcccatgcc aaccggttc atgtgctcgc cgaggcggca taaatcgccg tgacgatcag 14080
 cgggtccagt atcgaagtta ggctgggtaag agccgcgagc gatccttgaa gctgtccctg 14140
 atggtcgtca tctacctgcc tggacagcat ggcctgcaac gcgggcatcc cgatgccgcc 14200
 ggaagcgaga agaatacataa tggggaaggc catccagcct cgcgtcgcga acgccagcaa 14260
 gacgtagccc agcgcgtcgg ccgccatgcc ctgcttcac cccgtggccc gttgctcgcg 14320
 tttgctggcg gtgtccccgg aagaaatata tttgcatgtc ttagttcta tgatgacaca 14380

NruI

Figure 13U

aacccgcc agcgtcttgt cattggcgaa ttcgaacacg cagatgcagt cggggcggcg 14440
cgggtcccagg tccacttcgc atattaaggt gacgcgtgtg gcctcgaaca ccgagcgacc 14500
ctgcagcgac ccgcttaaca gcgtcaacag cgtgccgcag atcccgggca atgagatatg 14560
aaaaagcctg aactcaccgc gacgtctgtc gagaagtctt tgatcgaaaa gttcgacagc 14620
gtctccgacc tgatgcagct ctccggagggc gaagaatctc gtgctttcag cttcgatgta 14680
ggagggcgctg gatatgtcct gcgggtaaat agctgcgccg atggtttcta caaagatcgt 14740
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ggaattcagc gagagccctga cctattgcat ctcccgccgt gcacagggtg tcacgttgca 14860
agacctgcct gaaaccgaac tgcccgttgt tctgcagccg gtcgcggagg ccatggatgc 14920
PvuI
gatacgtgcg gccgatctta gccagacgag cgggttcggc ccatcggac cgcaaggaaat 14980
cggccaatac actacatggc gtgatttcat atgcgcgatt gctgatcccc atgtgtatca 15040
ctggcaaaact gtgatggacg acaccgtcag tgcgtccgtc gcgcaggctc tcgatgagct 15100
gatgctttgg gccgaggact gccccgaagt ccggcacctc gtgcacgcgg atttcggctc 15160
caacaaatgtc ctgacggaca atggccgcat aacagcggtc attgactgga gcgaggcgat 15220

Figure 13V

gttcgggggat tcccaatacg aggtcgccaa catcttcttc tggaggccgt ggttggcggg 15280
tatggagcag cagacgcgct acttcgagcg gaggcataccg gagcttgca gatacgcgcg 15340
gctccgggcg tatatgctcc gcattggtct tgaccaactc tatcagagct tggttgacgg 15400
caatttcgat gatgcagctt gggcgccaggg tcgatgcgac gcaatcgtcc gatccggagc 15460
cgggactgtc gggcgctacac aaatcgcccg cagaagcgcg gccgtctgga ccgatggctg 15520
tgtagaagta ctgcgcgata gtggaaacgg gagatggggg aggctaactg aaacacggaa 15580
ggagacaata ccggaaggaa cccgcgctat gacggcaata aaaagacaga ataaaaacga 15640
cgggtgttgg gtcgtttgtt cataaacgcg gggttcggtc ccagggtggtg cactctgtcg 15700
ataccccacc gagaccccat tggggccaat acgcccgcgt ttcttccttt tccccacccc 15760
accccccaag ttcgggtgaa ggcccagggc tcgcagccaa cgtcggggcg gcaggccctg 15820
ccatagccac tggccccctg ggttagggac ggggtcccc atgggggaatg gtttatgggt 15880
cgtgggggtt attattttgg gcgttgctg gggttcgtg cagactgga ctgagcagac 15940
agaccatgg tttttggatg gcctgggcat ggaccgcatg tactggcgcg acacgaacac 16000
cgggcgtctg tggctgcaa acacccccga cccccaaaa ccaccgcgcg gatttctggc 16060

Figure 13W

SaI

gtgccaagct agtcgaccaa

▲

16080

CTGTTGGGCTCGCGGTTGAGGACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAAC
 CCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGAT
 CGGAAAACCTCTCGACTGTTGGGGTGAGTACTCCCTCTCAAAGCGGGCATGACTTCTGCGCT
 AAGATTGTCAGTTTCCAAAAACGAGGAGGATTTGATATTACCTGGCCCCGCGGTGATGCCTTT
 GAGGGTGGCCGCGTCCATCTGGTCAGAAAAGACAATCTTTTGTGTCAAGCTTGAGGTGTGG
 CAGGCTTGAGATCTGGCCATACACTTGAGTGACAATGACATCCACTTTGCCTTTCTCTCCACAG
 GTGTCCACTCCCAGGTCCAACCTGCAGGTCGACTCTAGACCC

FIG. 14A

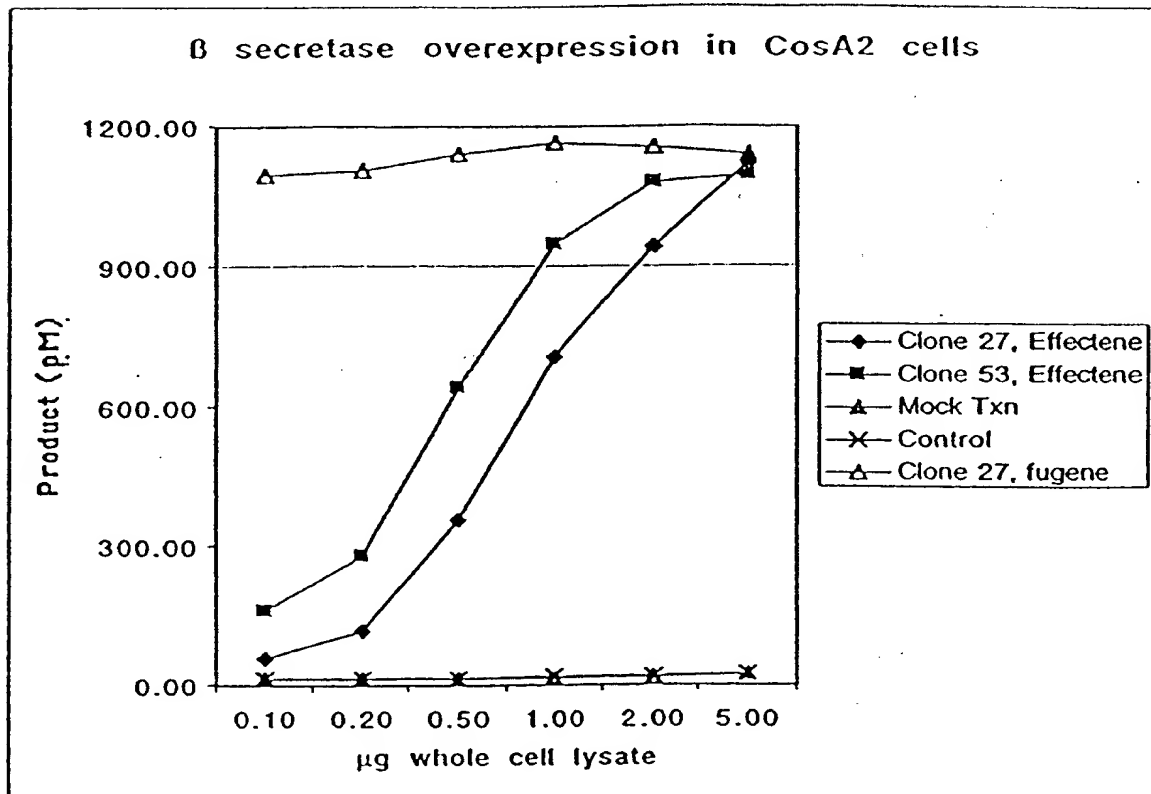


FIG. 14B

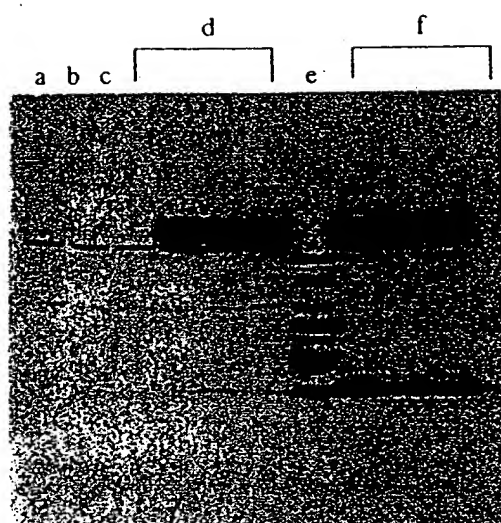


FIG. 15A

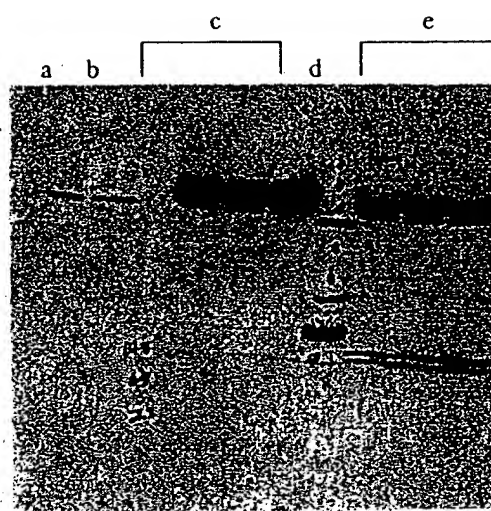


FIG. 15B

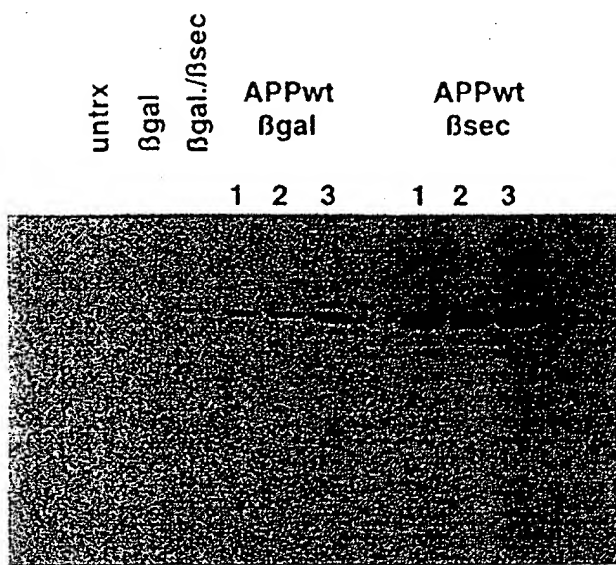


FIG. 16A

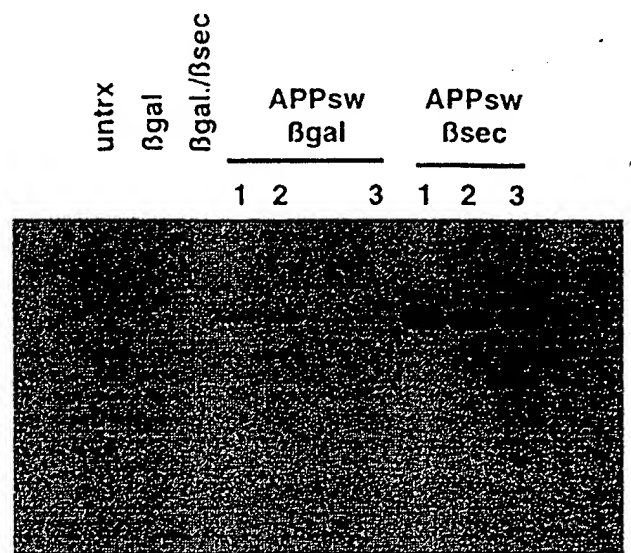


FIG. 16B

| | | | | | | |
|------|---------------|---|---|---------------|---|---|
| | APPwt βgal | | | APPwt βsec | | |
| βgal | 1 | 2 | 3 | 1 | 2 | 3 |



FIG. 17A

| | | | | | | |
|------|---------------|---|---|---------------|---|---|
| | APPsw βgal | | | APPsw βsec | | |
| βgal | 1 | 2 | 3 | 1 | 2 | 3 |



FIG. 17B

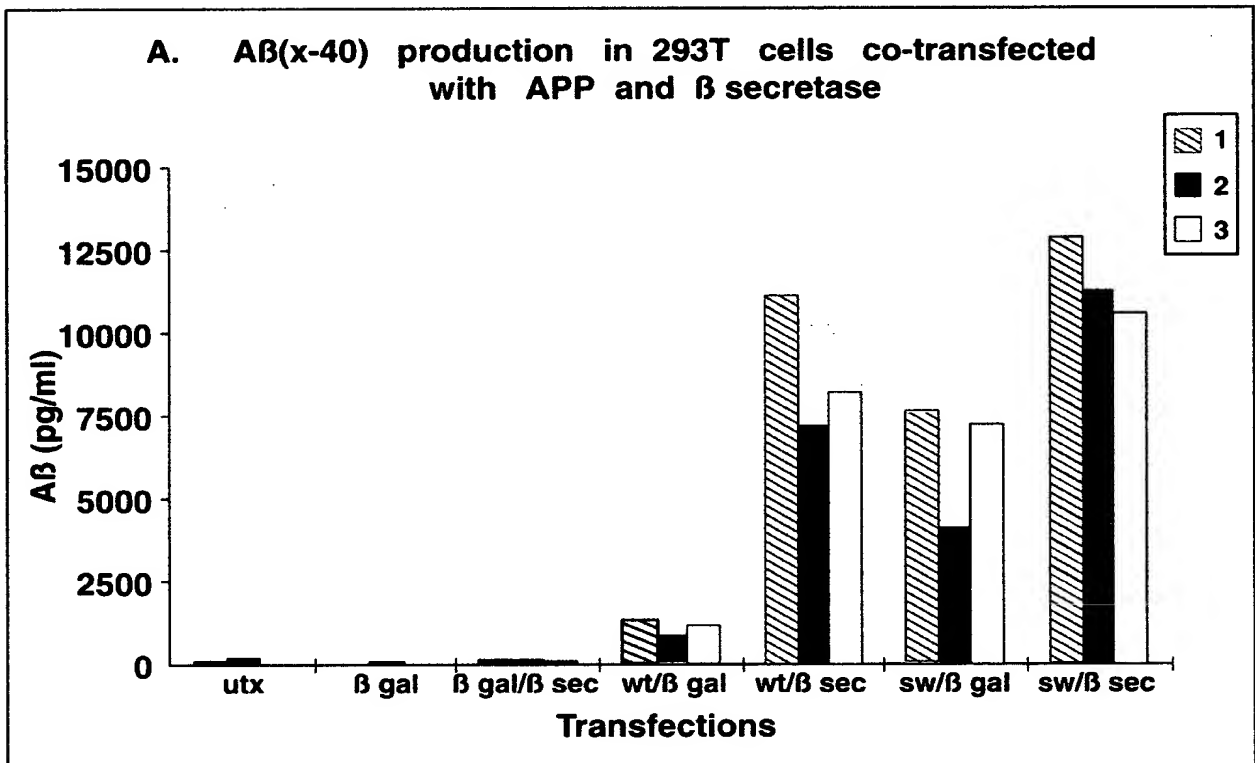


Fig. 18

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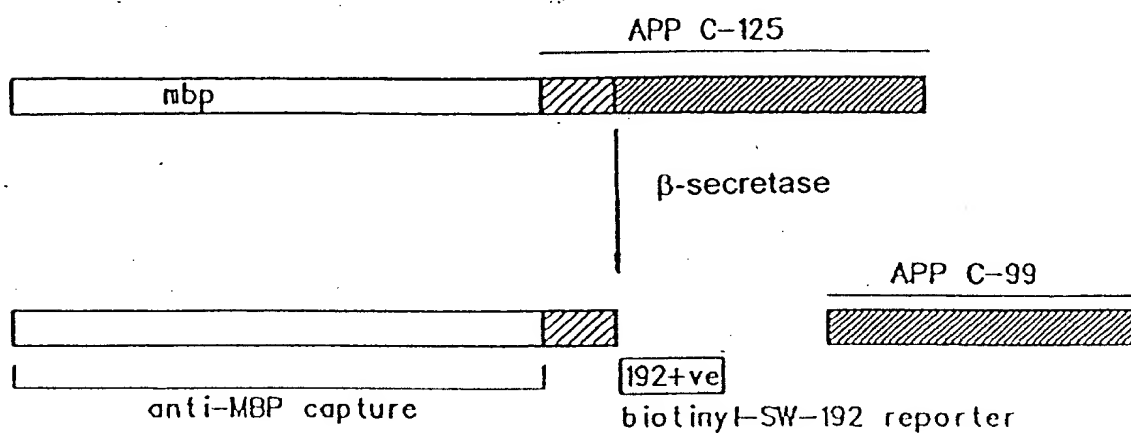


FIG. 19A

| | |
|--------------------|------------------------|
| Wild-Type Sequence |Val-Lys-Met-Asp... |
| Swedish Sequence |Val-Asn-Leu-Asp... |

FIG. 19B

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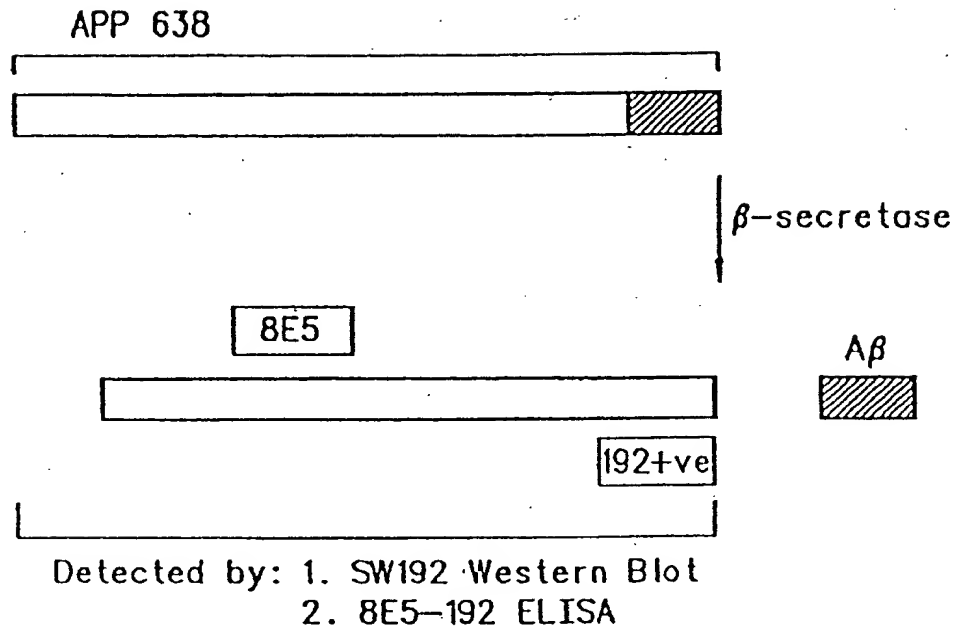


FIG. 20

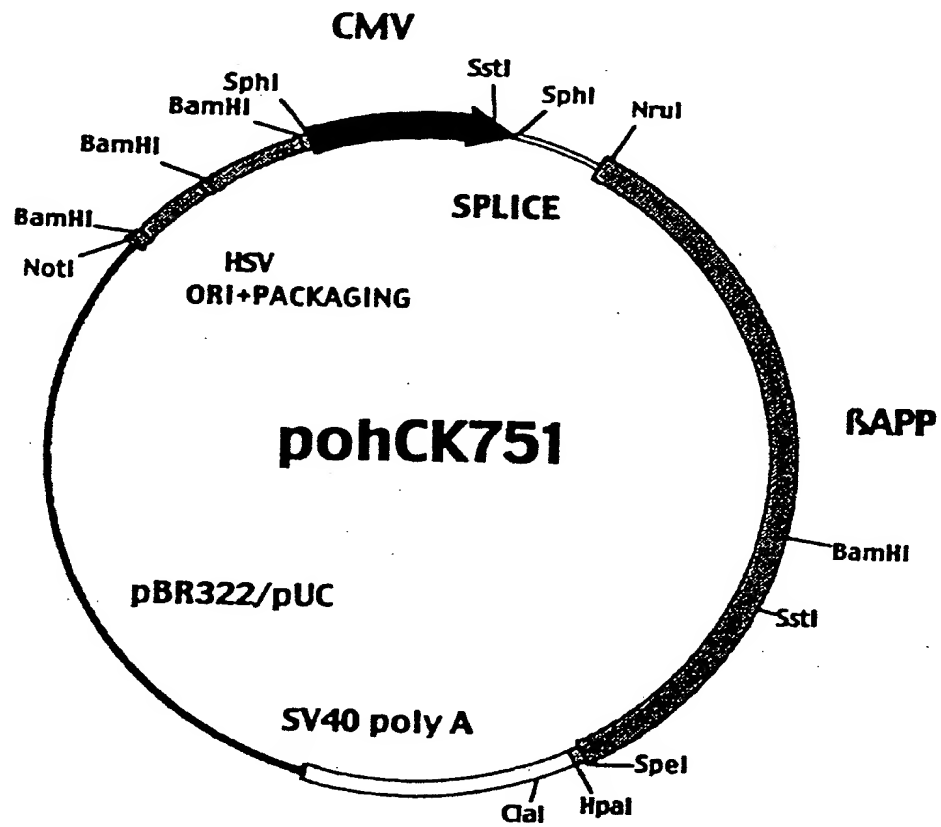


FIG. 21